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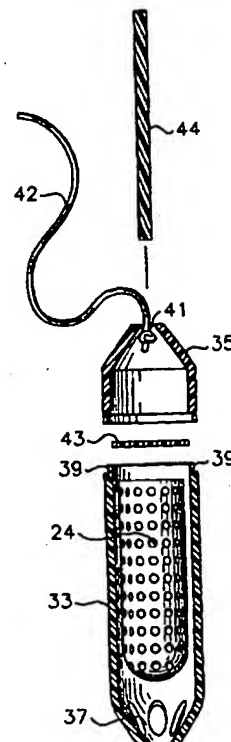
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*Before the expiration of the time limit for amending the
claims and to be republished in the event of the receipt of
amendments.*

(54) Title: METHOD AND APPARATUS FOR COLLECTING VAGINAL FLUID AND EXFOLIATED VAGINAL CELLS FOR
DIAGNOSTIC PURPOSES

(57) Abstract

Method and apparatus for collecting vaginal fluid and exfoliated vaginal cells for medical diagnostic purposes. An absorbent media (16, 25) is placed interlabially or intravaginally. Fluid is collected within the absorbent media (16, 25). The absorbent media (16, 25) is removed, and the fluid is extracted therefrom. For intravaginal collection, the absorbent media (16, 25) may be placed in a housing (31, 33, 35) having apertures (37) for permitting fluid to enter the inside of the housing (31, 33, 35). Medical diagnostic testing is performed on the extracted fluid.



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Method and Apparatus for Collecting
Vaginal Fluid and Exfoliated Vaginal
Cells for Diagnostic Purposes

Technical Field

5 This invention relates to generally medical diagnostic testing. The invention more particularly relates to the collection of vaginal fluids and exfoliated vaginal cells for diagnostic purposes.

Background Art

10 Currently, the vast majority of clinical diagnostic testing of biological fluids utilize serum and urine. It is believed that the United States Food and Drug Administration has not approved a clinical diagnostic test which utilizes any biological fluid other than whole
15 blood, serum, plasma, saliva or urine. Tears and sweat are other fluids being used for various non-FDA approved diagnostic purposes, although such uses have been very limited. These fluids are very different in composition and their uses in clinical medicine.

20 The use of gynecological tissue for cancer diagnostic purposes has been limited to the traditional PAP Test Cervical Scraping (PTCS method of collection) and the subsequent histological smears for cervical cancer screening. A chemical or immunochemical analysis of
25 non-menstrual vaginal fluid, menstrual fluid and/or the cellular extracts of menstrual fluid for the purpose of disease detection or patient well-being have not been exploited by the general medical community.

 There have been a number of articles written by
30 Dr. Matthew Freund and others which suggest that one may collect a large quantity of cervical and endometrial cells from menstrual fluids rather than through the traditional PTCS method. Dr. Freund found that both ectocervical and other cells collected from the menstrual fluid flow are
35 well preserved for standard laboratory cytological

procedures. They are similar in appearance to cells collected by current clinical methods, and give similar reactions to chemicals and stains, and may be analyzed by the same procedures as cervical smears for PAP testing.

5 Disclosure of Invention

In accordance with one form of this invention, there is provided a method for collecting vaginal fluid and exfoliated vaginal cells in menstrual fluid for medical diagnostic purposes. An absorbent media is placed
10 interlabially or intravaginally. Fluid is collected within the absorbent media. The absorbent media is removed, and the fluid is extracted therefrom. For intravaginal collection, the absorbent media may be placed in a housing having fluid receiving apertures prior to
15 insertion into the vagina. Medical diagnostic testing is performed on the extracted fluid.

Preferably the absorbent media used to collect vaginal fluid is an interlabia pad, such as the pads described in U.S. Patent Nos. 3,726,277; 3,983,873; and
20 4,196,562 issued to Hirschman and licensed to Athena Medical Corporation, assignee of the present invention, or the pad described in U.S. Patent No. 4,995,150 issued to Gerstenberger et al and assigned to Athena Medical Corporation. The Hirschman and Gerstenberger et al
25 patents are hereby incorporated herein by reference.

It is preferred that the absorbent media used to collect exfoliated vaginal cells from menstrual fluid be of a cylindrical shape similar to a tampon, but of a different construction and composition. Preferably, the
30 cylindrically shaped device includes an absorbent core which is at least partially surrounded by a porous matrix.

Over-the-counter kits may be provided so that the collection of the fluids may be done by the consumer in the privacy of her home.

35 The invention thus provides an improved method for collecting vaginal fluid and vaginal cells for

diagnostic purposes. The invention provides a non-invasive method for collecting vaginal fluid and vaginal cells for diagnostic purposes. The invention also provides an over-the-counter kit for collecting vaginal
5 fluid and vaginal cells for diagnostic purposes.

Brief Description of the Drawings

The subject matter which is regarded as the invention is set forth in the appended claims. The invention itself, however, together with further objects
10 and advantages thereof may be better understood in reference to the accompanying drawings in which:

FIG. 1 is a pictorial view of a fluid collection device which may be used in accordance with this invention and which is particularly useful in the collection of
15 vaginal fluid;

FIG. 2 is a pictorial view of a fluid collection device which may be used in accordance with this invention and is particularly useful in the collection of vaginal cells from menstrual fluid;

20 FIG. 3 is a sectional view of the device of FIG. 2;

FIG. 4 is a partial pictorial view of the device of FIG. 2 with a portion of the outer matrix removed;

FIG. 5 is a pictorial view of a collection kit
25 in accordance with the present invention;

FIG. 6 is a pictorial view of another collection kit in accordance with the present invention;

FIG. 7 is a pictorial view of a housing for the fluid collection device shown in FIG. 1 or FIG. 2; and

30 FIG. 8 is an exploded partial sectional view of the housing of FIG. 7.

Best Mode for Carrying Out the Invention

Vaginal fluid and vaginal cells originating from intravaginal secretions, such as menstrual fluid, can be
35 used to monitor several important clinical parameters,

including cervical cancer, candida, chlamydia, trichomonas, bacterial vaginosis, i.e. gardnerella, and the sexually transmitted diseases, including HIV, syphilis, gonorrhea, human papilloma virus, and herpes
5 infections. In addition, the fluid extract can be useful in measuring certain metabolic clinical parameters that have traditionally been limited to blood collections. Such parameters can be glucose, cholesterol, pituitary hormones, thyroid hormones, steroid hormones, therapeutic
10 drugs, drugs of abuse, nutritional markers (pre-albumin, etc.), fetal disease markers during pregnancy (placental protein markers) and levels of certain unknown metabolites that may be characterized by immunochemical (ELISA, RIA, FPIA, EMIT) or physical (NMR, HPLC, HPCE, HPTLC, GC-MS or
15 FTIR) diagnostic techniques.

The fluid collection apparatus of the subject invention may be an interlabia pad constructed in accordance with U.S. Patent Nos. 3,726,277 and 3,983,873 issued to Hirschman. The pad is formed from a fluid
20 absorbent material, preferably rayon, which has better properties for sample collection than compacted cellulose, which is used in tampons. Other natural or synthetic fibers with similar hydrodynamic properties to rayon could be used. The pad is adapted to be inserted into the
25 interlabia space by the user for absorbing vaginal discharges. The pad is securely retained in place despite substantial increases in its weight due to the absorption of vaginal fluids. The pad has been found to be safe and extremely comfortable for the user and is non-invasive.

30 Referring now more particularly to FIG. 1, an interlabia pad 15 includes an absorbent inner rope 16 covered by outer covering 18. The absorbent inner rope 16 may be made of the same absorbent material referred to above. A portion 20 of covering 18 extends along the side
35 rope 16 so as to provide a place for the user to grip the pad for insertion into and withdrawal from the interlabia space. Preferably opposing sides of the cover are sewn or

ultrasonically sealed together, depending on the type of material, as indicated along attachment line 22. The pad of FIG. 1 is more fully described in U.S. Patent No. 4,196,562 issued to Hirschman. It has been found that
5 the pad shown in FIG. 1 is useful in collecting vaginal fluids for diagnostic purposes.

FIGS. 2, 3 and 4 show an absorbent device 24 which has a cylindrical shape like a tampon, but has a different structure and function. Absorbent device 24
10 includes a soft inner core 25 made of a fluid absorbent material made of a highly absorbent, but extractable, material, such as rayon, cellulose, cotton or other natural or synthetic fibers. Core 25 is able to absorb at least five times its weight in fluid. Preferably, core 25
15 is made of rayon fibers to eliminate dehydration and trapping of cellular elements, which occur to a greater extent with compacted cellulose materials employed in tampons. Device 24 includes an outer covering 27 to enhance its stability and to permit fluid to freely pass
20 therethrough into core 25. Covering 27 is made of a highly porous material, such as sponge or nylon, and includes a visible matrix of pores 29 which allows for the collection of cellular debris without dehydration or inversible trapping within the matrix. The porous matrix
25 allows for a greater ease of extraction and high quality of cellular material obtained. Device 24 is inserted intravaginally, in close proximity to the cervix.

Device 24 is also useful as a vaginal fluid collection device, particularly, for collecting blood and
30 fluid from menstrual flow.

In cases where the fluid is to be collected intravaginally, the absorbent device 15 or 24 may be inserted into an elongated housing 31 having a plurality of fluid receiving apertures therein. This may be seen
35 better in reference to FIGS. 7 and 8. Elongated housing 31 includes a lower hollow portion 33 and an upper hollow portion 35. The lower portion 33 includes a plurality of

apertures 37 for permitting fluid to enter the inside of the housing. The inside of the housing receives absorbent device 15 or 24. The upper portion of the housing 35 is in the form of a cap. The cap is removably secured to the lower portion of the housing 33 by engagement with studs 39. The housing 31 with the absorbent material 24 received therein is inserted into the vagina for collecting fluids. Once the fluids are collected, the housing 31 is removed from the vagina, using pull string 42. Opening 41 is provided in the top of the cap. A rod or plunger 44 may be placed into opening 41 and pressed against plate or disc 43 within device 24 to compress the fluid laden absorbent device and thus, squeeze out the fluids. The fluids flow back through apertures 37 and into a collection vessel.

The pads 15 are preferably included as a part of a vaginal fluid collection kit 26, as shown in FIG. 5, containing shipping tubes 28, mailing labels 30 and instructions 31, all housed in box 32. Housing 33 may also be included in the kit 26. Kit 26 is preferably available over-the-counter or from a physician and may be conveniently used by the consumer in the privacy of her home. The pad is first inserted interlabially and remains inserted for a specified amount of time. When ready, the pad is dropped into a disposable sample container 28 containing extraction/preservative solution and is mailed to a laboratory for analysis. Thus there is provided a non-invasive, simple, convenient and private sample collection procedure which allows collection of vaginal fluids using the kit, with its attendant advantages over having to go to a physician's office or clinic for a cervical scrape, or for blood collection.

Device 24 is particularly adapted to collect exfoliated cells or other specimen materials from vaginal fluid. Device 24 is also preferably included in an exfoliated cell collection kit 34, as shown in FIG. 6. Kit 34 includes device 24 and sample vials 36 and 38,

containing an extraction buffer and/or preservative solution. The top of the sample vial is sealable. Device 24 and cups are received in box 40. Device 24 is inserted into the vaginal tract or labia and allowed to

5 collect/absorb for short periods or overnight. Device 24 is then removed by the user and placed in sample vial 36 containing the extraction buffer and preservative. The vial containing the specimen is then sealed and mailed to a testing laboratory. This technique is also a

10 non-invasive, convenient, simple and private method of sample collection. It is believed that the quantity of cells collected is greater and the collection is more consistent than that for the PTCS method. Use of the extraction buffer, preservative buffer, or both will vary

15 depending on the types of test desired. Additional material needed for mailing of biohazardous material may be added to the kit. Instructions which contain a patient information sheet to be filled out by the user to be mailed with the sample may also be added to the kit.

20 Both the PTCS and blood collection methods require a trained health professional to collect the samples and do not offer the advantages of privacy and non-invasiveness, as set forth above. In addition, when used for cervical cancer detection, the quality of cells

25 obtained by the method of this invention is comparable to or greater than that of the PTCS for diagnosing cervical cancer. Furthermore, it is believed that the consistency of the sample collection is inherently superior using teachings of this invention over PTCS. The PTCS method

30 can vary significantly in quality and quantity due to technique variations between health care technicians and the anatomical differences among patients. These variations in sample collection using the PTCS method are believed to be the main reason for the high false negative

35 rate among cervical cancer tests. The method of this invention does not rely on technique dependent procedures to obtain a representative sample, and as such, is less

likely to allow a false negative test to occur. In addition, the fluid sample contains certain cellular molecular components, i.e. hemoglobin, that can be measured and then used as internal qualitative markers to
5 address sample adequacy and standardization issues.

Thus there is provided a simple, inexpensive and convenient method for the collection of vaginal fluid and vaginal cells for diagnostic purposes. The method is non-invasive and kits may be purchased by the consumer
10 over the counter, resulting in far less expense and inconvenience to the consumer. In addition, it is believed that the diagnostic accuracy will be greatly enhanced, particularly for cervical cancer detection.

From the foregoing description of the preferred
15 embodiments of the invention, it will be apparent that many modifications may be made therein. It will be understood, however, that these embodiments of the invention are exemplifications of the invention only and that the invention is not limited thereto. It is to be
20 understood therefore that it is intended in the appended claims to cover all modifications that fall within the true spirit and scope of the invention.

Industrial Applicability

The way in which the invention is capable of
25 being exploited and the way in which it can be made and used will be apparent from the foregoing.

Claims

1. A method for collecting vaginal fluid and/or exfoliated vaginal cells for diagnostic purposes comprising the steps of:

- 5 placing a fluid absorbent media interlabially,
said fluid absorbent media being an interlabial pad;
collecting fluid in the interlabial pad;
removing the interlabial pad;
extracting fluid from the interlabial pad;
10 performing medical diagnostic testing on the
extracted fluid.

2. The method of claim 1, wherein said interlabia pad includes a major portion and a minor portion and wherein said fluid absorbent media is removed by gripping
15 said minor portion and removing said interlabia pad.

3. A method for collecting vaginal fluid and/or exfoliated vaginal cells for diagnostic purposes comprising the steps of:

- placing a fluid absorbent media intravaginally,
20 said absorbent media including an inner core and an outer
covering having a visible matrix of pores, said inner core
being able to absorb more than its weight in fluid;
 passing fluid through said visible matrix of
pores into said inner core and collecting fluid in the
25 absorbent inner core;
 removing the absorbent media;
 extracting fluid and cellular material from the
absorbent media;
 performing medical diagnostic testing on the
30 extracted fluid and cellular material.

4. A method as set forth in claim 3, wherein said fluid absorbent media is a cylindrically shaped device for intravaginal insertion.

5. A method as set forth in claim 4, wherein said inner core is made of rayon fibers.

6. A method for collecting vaginal fluid and/or exfoliated vaginal cells for diagnostic purposes utilizing a housing having plurality of fluid receiving apertures and a removable upper portion and utilizing an interlabia pad comprising the steps of:

removing the upper portion of the housing;
placing the interlabia pad inside the housing;
10 placing the housing containing the interlabia pad intravaginally;
collecting fluid in the interlabia pad;
removing the housing;
extracting fluid from the interlabia pad; and
15 performing medical diagnostic testing on the extracted fluid.

7. A method for collecting vaginal fluid and/or exfoliated vaginal cells for diagnostic purposes comprising the steps of:

20 placing a fluid absorbent media inside an elongated container having a plurality of apertures for fluid to enter, said container including a removable upper portion so as to facilitate the placing of the fluid absorbent media within said container and removal of said
25 fluid absorbent media from said container;
placing said container intravaginally;
collecting fluid in the absorbent media;
removing said container from the vagina;
extracting fluid from the absorbent media by
30 compressing said fluid absorbent media within said container so that fluid flows from the container out through the apertures;
performing medical diagnostic testing on the extracted fluid.

8. A method as set forth in claim 7, wherein said upper portion includes an aperture therein whereby a rod may be inserted therethrough for compressing said fluid absorbent media thereby extracting the fluid from the
5 absorbent media.

9. An apparatus for collecting vaginal fluid comprising:

a housing adapted to receive a fluid absorbent media;

10 said housing including a lower portion having a plurality of apertures therein for permitting vaginal fluid to enter into said housing;

said housing further including an upper portion forming a removable cap having an opening therein.

15 10. An apparatus for collecting vaginal fluid comprising:

a housing adapted to receive a fluid absorbent media;

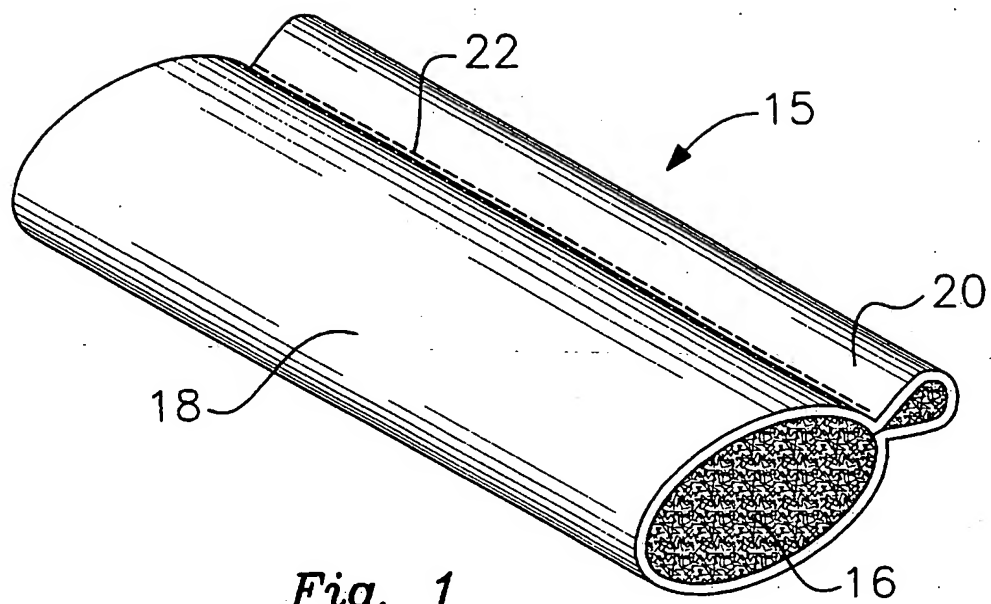
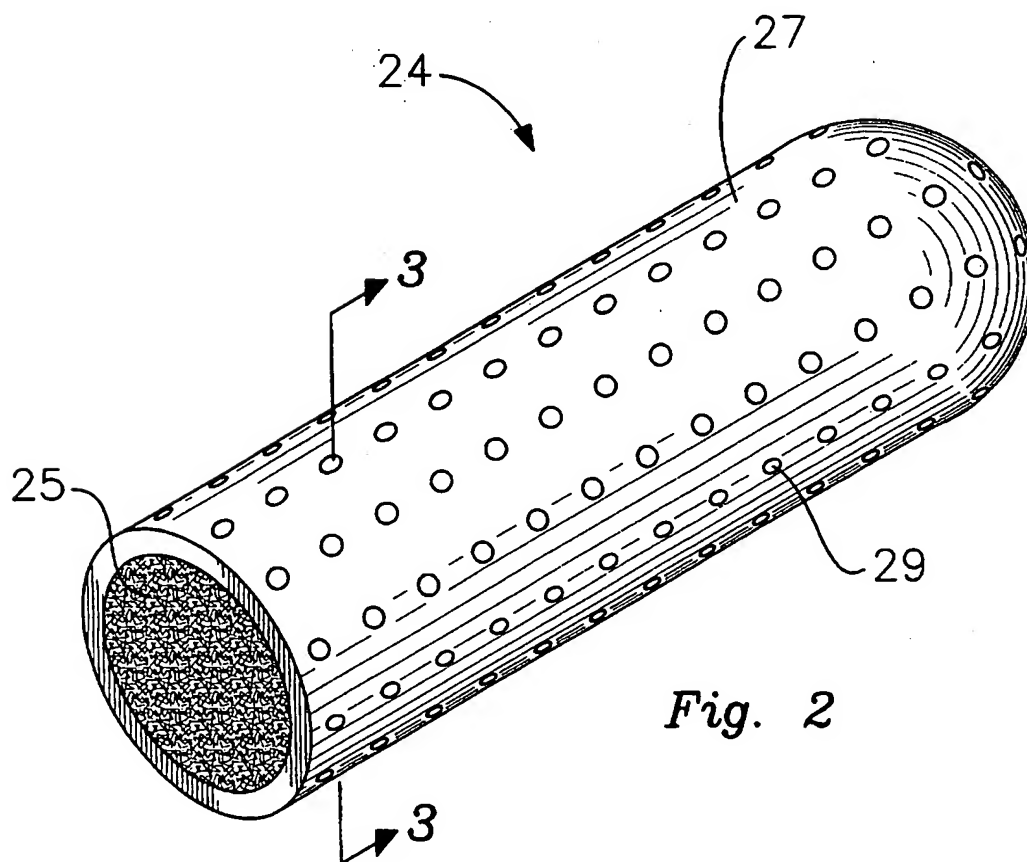
20 said housing including a lower portion having at least one aperture therein for permitting vaginal fluid to enter into said housing;

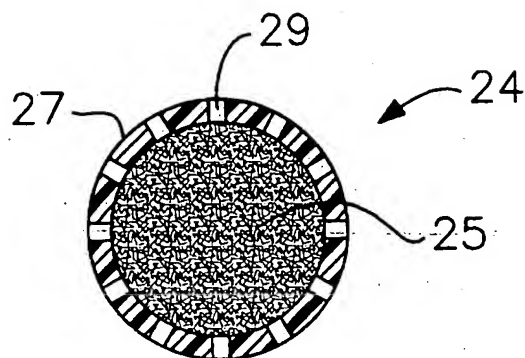
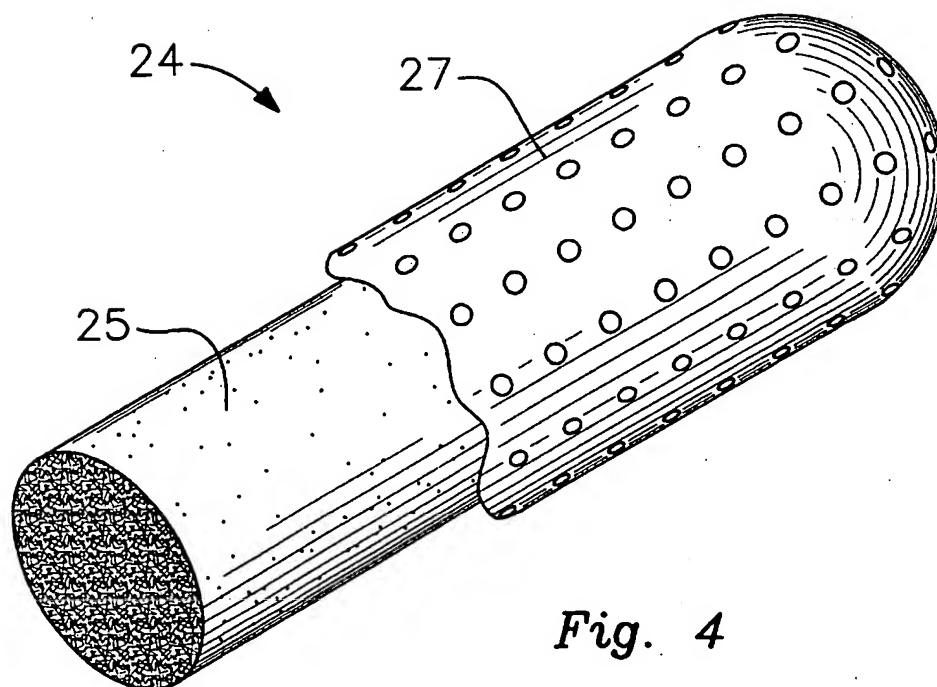
said housing further including an upper portion forming a removable cap having an opening therein; and

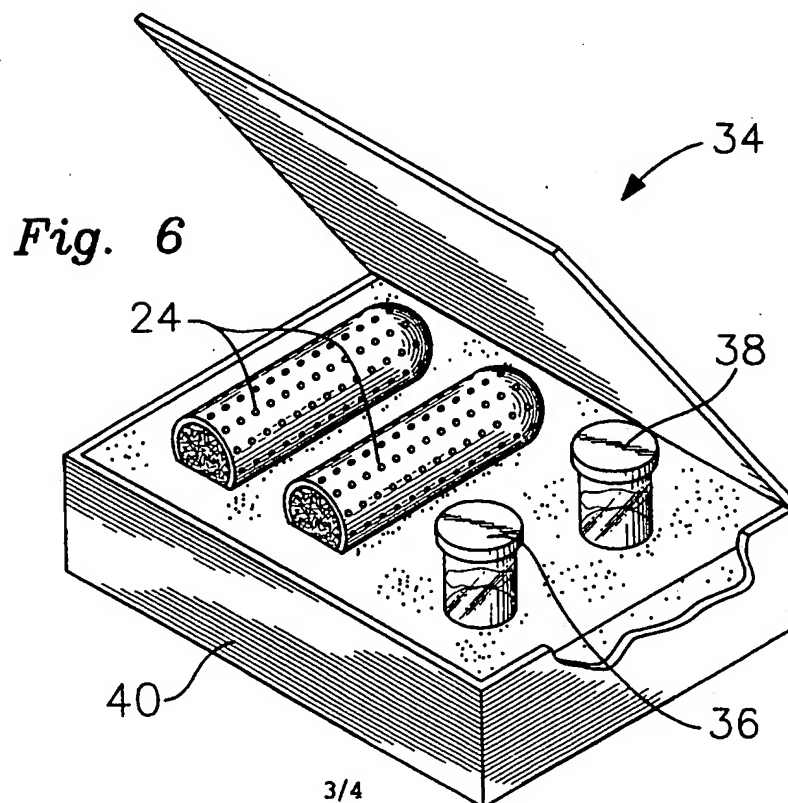
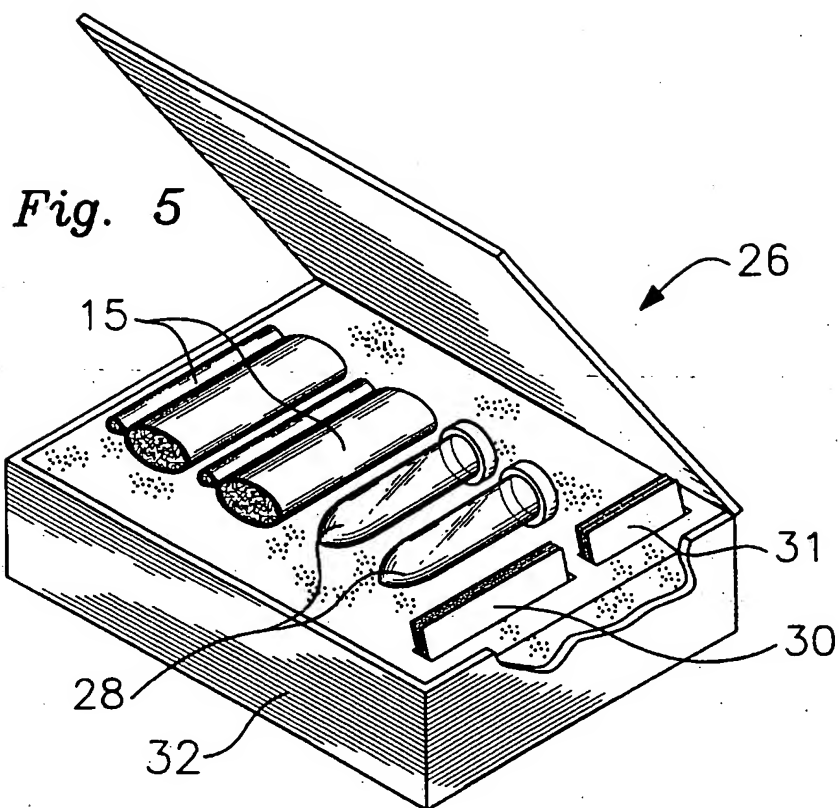
25 a rod adapted to be received through said opening in said cap for compressing the fluid absorbent media thereby causing said fluid from said fluid absorbent media to flow out of said housing through said at least one aperture in said lower portion.

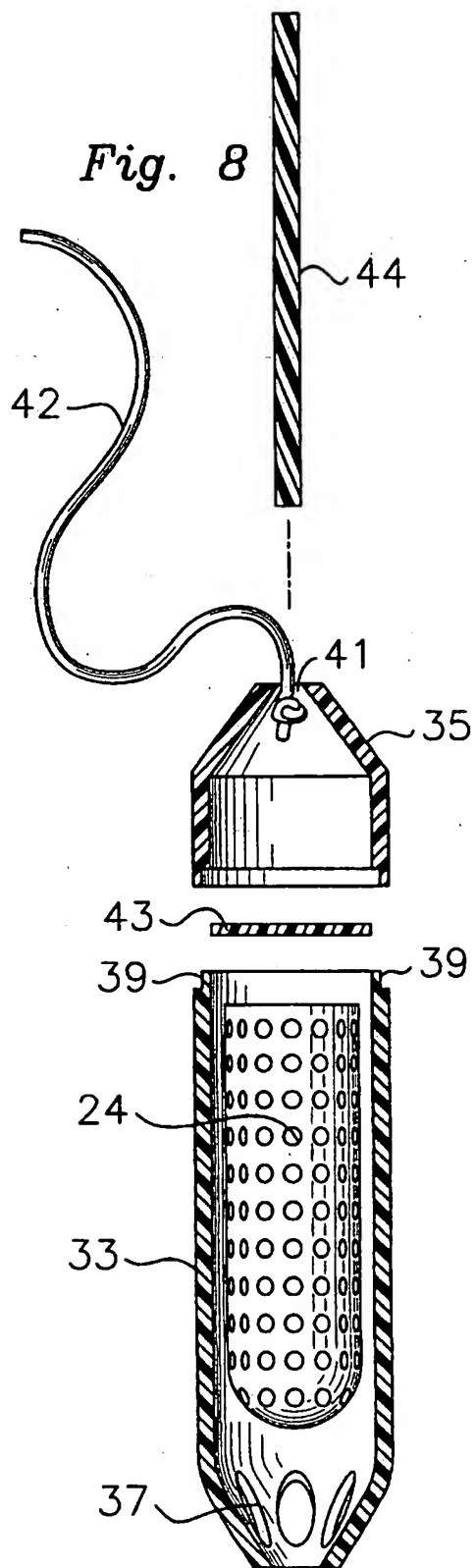
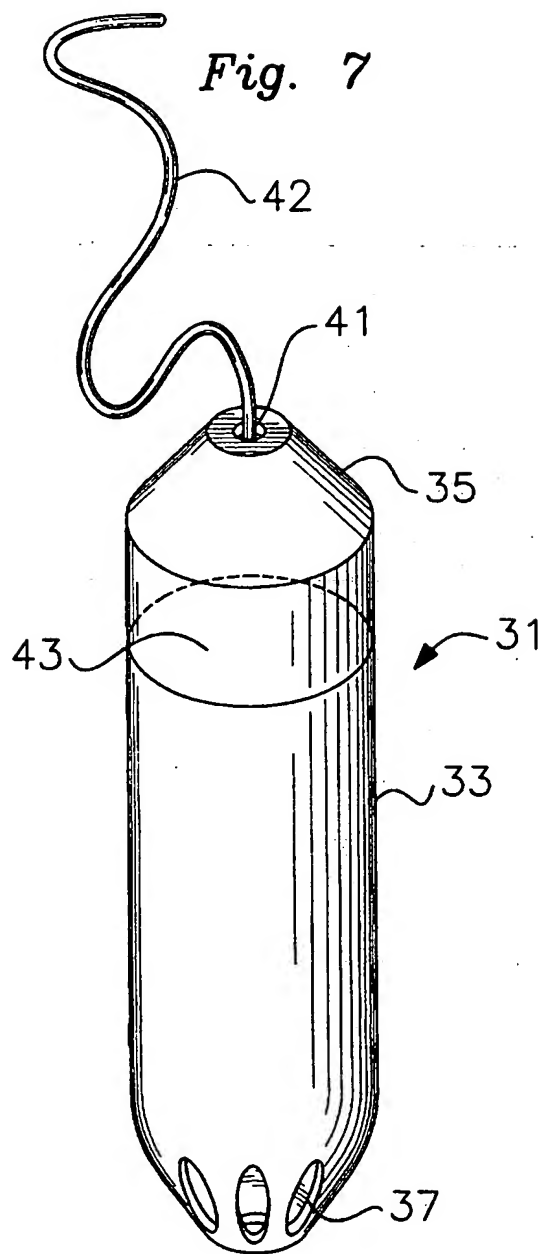
11. An apparatus as set forth in claim 10, further
30 comprising a plate located between said opening in said cap and the fluid absorbent media, said rod contacting said plate for compressing the fluid absorbent media.

12. A kit for collecting vaginal fluid and/or exfoliated vaginal cells comprising:
a box, said box receiving at least one fluid absorbent media, said fluid absorbent media being an
5 interlabial pad;
said box further receiving at least one container for receiving said interlabial pad after said interlabial pad has absorbed an amount of fluid and/or exfoliated cells for delivery of said saturated
10 interlabial pad to a medical diagnostic facility.
13. A kit as set forth in claim 12, wherein said container includes an amount of extraction solution.
14. A kit as set forth in claim 13, wherein said container includes an amount of preservative.
- 15 15. A kit for collecting vaginal fluid and/or exfoliated vaginal cells comprising:
a box, said box receiving at least one fluid absorbent media;
said fluid absorbent media including an inner
20 core and an outer covering;
said outer covering having a visible matrix of pores;
said box further receiving at least one container for receiving said absorbent media after said
25 absorbent media has absorbed an amount of fluid for delivery of said saturated absorbent media to a medical diagnostic facility.

*Fig. 1**Fig. 2*

*Fig. 3**Fig. 4*





INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61B10/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61B A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 788 985 A (MANNING PATRICK R ET AL) 6 December 1988	1,6,7,9, 10
X	see the whole document	3,4
A	US 3 850 160 A (DENSON J) 26 November 1974	1,6,7,9, 10
X	see the whole document	3,4
A	US 4 945 921 A (OKIMOTO PAUL M) 7 August 1990	1,3,4, 7-12,15
X	see the whole document	
X	EP 0 610 951 A (KIMBERLY CLARK CO) 17 August 1994	9
A	see the whole document	10

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

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information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4788985 A	06-12-88	US 4465078 A AU 1915483 A JP 59082835 A	14-08-84 05-04-84 14-05-84
US 3850160 A	26-11-74	AU 6561474 A BE 811037 A DE 2406416 A FR 2216975 A GB 1455107 A JP 50041378 A LU 69397 A NL 7402032 A	14-08-75 14-08-74 17-10-74 06-09-74 10-11-76 15-04-75 01-10-74 19-08-74
US 4945921 A	07-08-90	US 4784158 A AU 2112388 A EP 0304321 A JP 1094832 A	15-11-88 23-02-89 22-02-89 13-04-89
EP 0610951 A	17-08-94	BR 9400418 A CA 2095553 A JP 6245957 A US 5542914 A ZA 9400131 A	23-08-94 13-08-94 06-09-94 06-08-96 19-08-94